Appendix 1: Supplemental material

Exclusions

We enrolled 2088 patients in ARBs CORONA I. The following patients were excluded from the current analysis.

- Acute COVID-19 readmissions (n=37)
- Emergency Room admissions without hospitalization (n=125)
- Patients admitted to hospital but not due to acute COVID-19 (n=220)
- Patients with unknown discharge outcome or currently still hospitalized (n=19)
- Patients from sites which only enrolled ICU patients (Alberta; n=350)

Alberta site was different from the other participating sites in that it only enrolled patients who were admitted to ICU. Because the percentage of data from Alberta in ARBs CORONA I varied across waves (13%, 28% and 17% in waves 1, 2 and 3 respectively), the inclusion of Alberta site would thus confound and skew the crude results (for example, with the inclusion of Alberta data, ICU admission rate became 47%, 55% and 44% in waves 1, 2 and 3 respectively).

Relevant variables captured on ARBs CORONA I CRF

Data were collected by ARBs CORONA Research Coordinators at each site on specifically designed electronic Case Report Forms (CRF) and entered into a REDCap database. The variables selected for inclusion in the CRF were pathogen positivity, baseline characteristics (age, sex, co-morbidities (chronic cardiac, and pulmonary kidney disease, hypertension, diabetes, liver disease, chronic neurologic disease, malignancy, chronic hematologic disease, AIDS/HIV, rheumatologic disease, dementia and malnutrition), COVID-19-vaccine use, vital signs (first available data within 24 hours of admission: temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, oxygen saturation by pulse oximetry), leukocyte (WBC) count, hemoglobin, creatinine, antiviral agents, antibiotics, corticosteroids and type of corticosteroid, and antifungal agents. Outcomes were 28-day mortality, in-hospital mortality, admission to ICU, ventilation, vasopressors and RRT while hospitalized, and hospital length of stay, date of onset and completion of ventilation, vasopressors (Norepinephrine, Levosimendan, Dopamine, Epinephrine, Dobutamine, Vasopressin, Milrinone, Other) and RRT.

COVID-19 therapies were recorded based on literature that showed efficacy and/or their use in sites.

Antiviral agent

- Ribavirin
- Lopinavir/Ritonavir
- Interferon alpha
- Interferon beta
- Neuraminidase inhibitor
- Other, specify

Antibiotic (Y/N)

Corticosteroid (Y/N)

Type and dose

Antifungal agent (Y/N)

Details on days alive and free (DAF) of invasive mechanical ventilation, vasopressors and RRT

The days alive and free of ventilation, vasopressors and RRT calculation presents use of these therapies while adjusting for deaths in the first 14 days because many patients die within the first 14 days (1-5). So, if we only reported duration of ventilation in a ventilated patient who died on day 2, the short duration of ventilation is biased by the early death. For patients who survived the first 14 days, DAF was simply the total number of the days free from these therapies. Since mortality was a competing risk for the use of vasopressors, ventilation and RRT, patients who died within 14 days were assigned a zero DAF to increase the penalty for non-survival (6). We calculated DAF over 14 days as in other trials in the critically ill (7).

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Statistical details on 0-1 inflated beta regression

The observed DAF data exhibited a U-shape distribution, with most data concentrated at 0 and 14. We thus used 0-1 inflated beta regression (1) to model the data. Prior work (2,3) on DAF data have also used such an approach.

DAF was expressed as proportion of days (i.e., divided by 14) in the regression model and then back transformed for interpretation. The R package *gamlss* was used to fit a 0-1 inflated beta regression model to the data. The default logit and log link functions were used for the components of the model. Given that the regression model has adjusted for covariates, we computed the marginal mean DAF of each wave by averaging the model predictions obtained from the *predict* function (i.e., fixed wave at a specific value and integrating over the remaining covariates). Estimated mean difference between waves was obtained by taking the difference between the marginal means. 95% confidence intervals were obtained using 1000 bootstrap samples. P values for the comparisons between waves were obtained by resampling under the null hypothesis that there was no difference between waves (1000 samples).

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ARBs CORONA I study investigators

British Columbia:

St. Paul's Hospital, Vancouver, BC, Can.: Drs. James A. Russell, Nadia Khan, John Boyd, Keith R. Walley, Anita Palepu, Adeera Levin. Centre for Health Evaluation and Outcomes Science (CHEOS), St. Paul's Hospital, Vancouver, BC, Can.: Drs. Joel Singer, Terry Lee. British Columbia Women's and Children's Hospital, Vancouver, BC, Can.: Dr. Srinivas Murthy. Vancouver General Hospital, Vancouver, BC, Can.: Drs. David Sweet, Karen Tran. Royal Columbian Hospital, New Westminster, BC, Can.: Dr Steve Reynolds. Surrey Memorial Hospital, Surrey, BC, Can.: Dr. Greg Haljan. British Columbia Centres for Disease Control: Dr. David Patrick.

Province of Quebec (PQ):

CHUS, Sherbrooke, PQ, Can.: Dr. Francois Lamontagne. McGill University Health Centre, Montreal, PQ, Can.: Dr. Matthew P. Cheng, Dr. Todd C. Lee.

Ontario:

Sunnybrook Hospital, Toronto, Ont. Can.: Dr. Robert Fowler. Mount Sinai Hospital, Toronto, Ont. Can.: Dr. Allison McGeer. St Michael's Hospital, Toronto, Ont., Can.: Drs. John Marshall, Art Slutsky. Kingston General Hospital, Kingston, Ont., Can.: Drs. David Maslove, Santiago Perez Patrigeon. University of Ottawa, Ottawa, Ont., Can.: Dr. Kevin Burns.

Manitoba:

Winnipeg Health Sciences Centre, Winnipeg, Man., Can.: Dr. Anand Kumar.

Alberta:

Foothills Hospital, Calgary, Alberta, Can.: Dr. Brent Winston.

University of Alberta, Edmonton, Alta., Can.: Dr. Oleksa Rewa.

USA:

University of Pennsylvania, Philadelphia, Pa., USA: Dr. Michael Harhay.

The following persons and institutions participated in the ARBs CORONA I Study: **Steering Committee** – J.A. Russell (chair), Genevieve Rocheleau (former project manager), Puneet Mann (project manager), D. Sweet, G. Haljan, M. Cheng, D. C. Vinh, T. Lee, F. Lamontagne, B. Winston, O. Rewa, J. Marshall, A. McGeer, R. Fowler, David Maslove, Santiago Perez Patrigeon. **Management Committee** - J.A. Russell (chair), Genevieve Rocheleau (project manager), Puneet Mann (project manager), Karen Tran, Joel Singer. **Data Management** – J. Singer, T. Lee.

CLINICAL CENTERS AND ARBS CORONA I INVESTIGATORS:

Canada. British Columbia: St. Paul's Hospital (Coordinating Centre) - J.A. Russell, K.R. Walley, J. Boyd, T. Lee, J. Singer. Vancouver General Hospital - D. Sweet, K. Tran. Royal Columbian Hospital - S. Reynolds. Surrey Memorial Hospital - G. Haljan. Quebec: McGill University Centre Hospital - M.P. Cheng, D.C. Vinh, TC Lee. Sherbrooke - F. Lamontagne.

Alberta: Calgary General Hospital - B. Winston, University of Alberta - O. Rewa. Ontario: St. Michael's Hospital - J. Marshall, A. Slutsky. Mount Sinai Hospital - A. McGeer, V. Sivanantham. Sunnybrook and Women's College Health Science Centre - R. Fowler. Kingston General Hospital - David Maslove, Santiago Perez Patrigeon.

Table S1: Number of patients by province and site

			Wave	
Variable	All (n=1337)	1st (n=520)	2nd (n=572)	3rd (n=245)
Province, n (%)				
BC	695 (52.0)	136 (26.2)	361 (63.1)	198 (80.8)
ON	272 (20.3)	24 (4.6)	201 (35.1)	47 (19.2)
QC	370 (27.7)	360 (69.2)	10 (1.7)	0 (0.0)
Site, n (%)				
St. Paul's Hospital, Vancouver, BC	213 (15.9)	66 (12.7)	92 (16.1)	55 (22.4)
Vancouver General Hospital, Vancouver, BC	320 (23.9)	55 (10.6)	157 (27.4)	108 (44.1)
Surrey Memorial Hospital, Surrey, BC	162 (12.1)	15 (2.9)	112 (19.6)	35 (14.3)
Humber River Hospital, North York, ON	51 (3.8)	0 (0.0)	45 (7.9)	6 (2.4)
Kingston General Hospital, Kingston, ON	18 (1.3)	4 (0.8)	13 (2.3)	1 (0.4)
Mount Sinai Hospital, Toronto, ON	142 (10.6)	20 (3.8)	82 (14.3)	40 (16.3)
Sunnybrook Hospital, Toronto, ON	61 (4.6)	0 (0.0)	61 (10.7)	0 (0.0)
McGill University Health Centre, Montreal, QC	258 (19.3)	258 (49.6)	0 (0.0)	0 (0.0)
Centre hospitalier universitaire de Sherbrooke, QC	112 (8.4)	102 (19.6)	10 (1.7)	0 (0.0)

Table S2: Co-morbidities of patients admitted with acute COVID-19

			Wave		
Variable	All (n=1337)	1st (n=520)	2nd (n=572)	3rd (n=245)	P
Co-morbidities, n (%)					
Any of the four below	899/1331 (67.5)	370/518 (71.4)	381/569 (67.0)	148/244 (60.7)	0.011
Chronic cardiac disease	353/1324 (26.7)	166/517 (32.1)	141/565 (25.0)	46/242 (19.0)	< 0.001
Chronic kidney disease	199/1332 (14.9)	82/519 (15.8)	94/570 (16.5)	23/243 (9.5)	0.029
Hypertension	709/1330 (53.3)	295/519 (56.8)	299/569 (52.5)	115/242 (47.5)	0.050
Diabetes	424/1330 (31.9)	170/518 (32.8)	183/568 (32.2)	71/244 (29.1)	0.574
Chronic pulmonary disease	214/1327 (16.1)	102/519 (19.7)	81/567 (14.3)	31/241 (12.9)	0.018
Liver disease	56/1331 (4.2)	21/517 (4.1)	21/570 (3.7)	14/244 (5.7)	0.400
Chronic neurological disorder	147/1330 (11.1)	68/519 (13.1)	56/569 (9.8)	23/242 (9.5)	0.161
Malignant neoplasm	101/1324 (7.6)	43/517 (8.3)	36/564 (6.4)	22/243 (9.1)	0.318
Chronic hematologic disease	60/1330 (4.5)	30/518 (5.8)	25/569 (4.4)	5/243 (2.1)	0.068
AIDS / HIV	10/1305 (0.8)	4/491 (0.8)	2/570 (0.4)	4/244 (1.6)	0.154
Rheumatologic disorder	150/1330 (11.3)	41/517 (7.9)	76/570 (13.3)	33/243 (13.6)	0.009
Dementia	154/1328 (11.6)	100/516 (19.4)	42/569 (7.4)	12/243 (4.9)	<0.001
Malnutrition	11/1331 (0.8)	8/517 (1.5)	3/570 (0.5)	0/244 (0.0)	0.062

P value was based on Chi-square test or Fisher's exact test as appropriate.

Table S3: COVID-19 therapies during the hospital course.

			Wave		
Variable, n (%)	All (n=1337)	1st (n=520)	2nd (n=572)	3rd (n=245)	Р
Antiviral agent	211/1330 (15.9)	72/516 (14.0)	106/569 (18.6)	33/245 (13.5)	0.057
Lopinavir/Ritonavir	13/1330 (1.0)	13/516 (2.5)	0/569 (0.0)	0/245 (0.0)	<0.001
Remdesivir	128/1330 (9.6)	8/516 (1.6)	96/569 (16.9)	24/245 (9.8)	<0.001
Antibiotic	1119 (83.7)	434 (83.5)	486 (85.0)	199 (81.2)	0.408
Corticosteroid	882 (66.0)	160 (30.8)	499 (87.2)	223 (91.0)	<0.001
Dexamethasone	756 (56.5)	56 (10.8)	482 (84.3)	218 (89.0)	<0.001
Antifungal agent	73 (5.5)	34 (6.5)	23 (4.0)	16 (6.5)	0.135

P value was based on Chi-square test or Fisher's exact test as appropriate.

Table S4: Mortality in patients hospitalized with acute COVID-19 in unadjusted and adjusted analyses.

		28-day m	ortality		In-hospital death					
	Unadjusted analysis (n	n=1337)	Adjusted analysis (r	=1259)	Unadjusted analysis (n=1337)	Adjusted analysis (r	า=1259)		
Variable	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P		
Wave										
2 vs 1	0.94 (0.63, 1.39)	0.750	0.89 (0.61, 1.29)	0.528	0.82 (0.59, 1.14)	0.246	0.84 (0.58, 1.20)	0.333		
3 vs 1	0.43 (0.24, 0.78)	0.005	0.46 (0.26, 0.81)	0.007	0.41 (0.25, 0.69)	< 0.001	0.46 (0.27, 0.80)	0.005		
3 vs 2	0.46 (0.27, 0.79)	0.004	0.52 (0.29, 0.91)	0.022	0.50 (0.31, 0.81)	0.005	0.56 (0.33, 0.94)	0.028		
Male			1.06 (0.74, 1.52)	0.733			1.29 (0.92, 1.82)	0.139		
Age (per 10 years increase)			2.23 (1.91, 2.61)	<0.001			1.99 (1.73, 2.30)	< 0.001		
SBP (per 10mm Hg increase)			0.93 (0.86, 1.00)	0.058			0.93 (0.87, 1.00)	0.051		
Chronic kidney disease			0.94 (0.56, 1.59)	0.823			0.88 (0.53, 1.45)	0.609		
Chronic cardiac disease			0.92 (0.63, 1.33)	0.642			0.97 (0.68, 1.39)	0.882		
Diabetes			1.57 (1.10, 2.25)	0.013			1.43 (1.02, 2.00)	0.037		
Hypertension			0.85 (0.58, 1.25)	0.403			0.93 (0.65, 1.33)	0.683		
Heart rate (per 10 beats/minute increase)			1.18 (1.08, 1.29)	<0.001			1.11 (1.02, 1.21)	0.014		
Creatinine (per log µmol/L increase)			1.86 (1.25, 2.75)	0.002			1.91 (1.32, 2.76)	<0.001		
Oxygen saturation - SaO2 (per 5 % increase)			0.79 (0.71, 0.88)	<0.001			0.80 (0.72, 0.89)	<0.001		

All analyses have adjusted for site as a random effect.

Odds ratio of <1 implied less likely to experience the outcome.

Table S5: Use of mechanical ventilation, renal replacement therapy (RRT) and vasopressors in patients hospitalized with acute COVID-19 in unadjusted and adjusted analyses.

	Mechanical	Mechanical ventilation - while hospitalized			RR	r - while l	hospitalized		Use of vasopressors - while hospitalized			
	Unadjusted analysis	(n=1337)	Adjusted analysis (n=1259)	Unadjusted analysis (r	=1320)	Adjusted analysis (r	n=1244)	Unadjusted analysis	n=1337)	Adjusted analysis (n=1259)
Variable	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	Р	Odds ratio (95% CI)	P	Diff (95% CI)	P	Diff (95% CI)	P
Wave												
2 vs 1	0.56 (0.34, 0.93)	0.023	0.58 (0.42, 0.80)	< 0.001	0.81 (0.47, 1.41)	0.463	0.53 (0.28, 1.02)	0.058	0.67 (0.43, 1.07)	0.092	0.63 (0.40, 0.98)	0.042
3 vs 1	0.37 (0.21, 0.65)	< 0.001	0.34 (0.22, 0.54)	< 0.001	0.32 (0.12, 0.84)	0.022	0.17 (0.05, 0.63)	0.008	0.51 (0.30, 0.85)	0.009	0.43 (0.25, 0.73)	0.002
3 vs 2	0.66 (0.43, 1.01)	0.056	0.59 (0.38, 0.92)	0.021	0.39 (0.15, 1.03)	0.056	0.33 (0.09, 1.18)	0.087	0.75 (0.51, 1.12)	0.165	0.69 (0.45, 1.05)	0.084
Male			1.44 (1.05, 1.96)	0.022			1.11 (0.57, 2.17)	0.764			1.61 (1.18, 2.21)	0.003
Age (per 10 years increase)			0.83 (0.75, 0.92)	<0.001			0.73 (0.57, 0.92)	0.008			0.91 (0.82, 1.01)	0.071
SBP (per 10mm Hg increase)			1.01 (0.94, 1.07)	0.855			1.14 (1.01, 1.30)	0.038			0.94 (0.88, 1.00)	0.063
Chronic kidney disease			0.55 (0.31, 0.97)	0.039			0.41 (0.16, 1.09)	0.073			0.49 (0.28, 0.87)	0.014
Chronic cardiac disease			0.86 (0.60, 1.24)	0.425			1.82 (0.91, 3.65)	0.091			0.97 (0.67, 1.39)	0.858
Diabetes			1.49 (1.09, 2.04)	0.013			1.23 (0.65, 2.33)	0.533			1.31 (0.96, 1.80)	0.091
Hypertension			1.20 (0.86, 1.69)	0.290			2.69 (1.15, 6.27)	0.022			1.14 (0.81, 1.59)	0.460
Heart rate (per 10 beats/minute increase)			1.05 (0.98, 1.13)	0.174			1.01 (0.87, 1.18)	0.879			1.08 (1.00, 1.16)	0.041
Creatinine (per log µmol/L increase)			1.52 (1.07, 2.16)	0.019			8.97 (4.88, 16.49)	<0.001			1.71 (1.21, 2.43)	0.003
Oxygen saturation - SaO2 (per 5 % increase)			0.75 (0.68, 0.82)	<0.001			0.88 (0.73, 1.04)	0.141			0.75 (0.68, 0.83)	<0.001

All analyses have adjusted for site as a random effect.

Odds ratio of <1 implied less likely to experience the outcome.

Table S6: Use of mechanical ventilation, renal replacement therapy (RRT) and vasopressors over 14 days in patients hospitalized with acute COVID-19 in unadjusted and adjusted analyses.

	Mechani	Mechanical ventilation - first 14 days				RRT- first	14 days		Use of vasopressors - first 14 days			
	Unadjusted analysis	(n=1337)	Adjusted analysis (n=1259)	Unadjusted analysis (r	=1315)	Adjusted analysis (r	n=1241)	Unadjusted analysis (n=1335)	Adjusted analysis (n=1258)
Variable	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Diff (95% CI)	P	Diff (95% CI)	P
Wave												
2 vs 1	0.57 (0.35, 0.93)	0.024	0.58 (0.42, 0.80)	< 0.001	0.90 (0.45, 1.82)	0.778	0.54 (0.23, 1.27)	0.157	0.68 (0.43, 1.07)	0.097	0.62 (0.39, 0.98)	0.042
3 vs 1	0.36 (0.21, 0.62)	< 0.001	0.33 (0.21, 0.53)	< 0.001	0.48 (0.16, 1.39)	0.175	0.25 (0.06, 1.02)	0.054	0.51 (0.31, 0.85)	0.010	0.44 (0.26, 0.74)	0.002
3 vs 2	0.63 (0.41, 0.97)	0.036	0.57 (0.36, 0.90)	0.016	0.53 (0.19, 1.43)	0.207	0.46 (0.12, 1.75)	0.255	0.75 (0.50, 1.13)	0.166	0.70 (0.46, 1.08)	0.108
Male			1.42 (1.04, 1.94)	0.028			0.97 (0.46, 2.02)	0.927			1.59 (1.16, 2.17)	0.004
Age (per 10 years increase)			0.83 (0.75, 0.93)	< 0.001			0.66 (0.51, 0.86)	0.002			0.92 (0.83, 1.02)	0.109
SBP (per 10mm Hg increase)			1.00 (0.94, 1.07)	0.897			1.14 (0.99, 1.31)	0.072			0.94 (0.88, 1.00)	0.051
Chronic kidney disease			0.52 (0.29, 0.93)	0.028			0.58 (0.21, 1.65)	0.308			0.47 (0.26, 0.84)	0.011
Chronic cardiac disease			0.84 (0.58, 1.21)	0.348			2.22 (1.03, 4.80)	0.042			0.95 (0.66, 1.37)	0.785
Diabetes			1.48 (1.08, 2.03)	0.015			1.00 (0.49, 2.06)	0.992			1.32 (0.96, 1.81)	0.090
Hypertension			1.18 (0.84, 1.66)	0.340			3.36 (1.25, 8.98)	0.016			1.09 (0.77, 1.53)	0.626
Heart rate (per 10 beats/minute increase)			1.05 (0.98, 1.14)	0.160			0.98 (0.83, 1.16)	0.823			1.08 (1.01, 1.17)	0.034
Creatinine (per log µmol/L increase)			1.57 (1.11, 2.24)	0.011			7.54 (4.00, 14.19)	<0.001		·	1.77 (1.25, 2.52)	0.001
Oxygen saturation - SaO2 (per 5 % increase)			0.74 (0.68, 0.82)	<0.001			0.88 (0.72, 1.08)	0.221			0.75 (0.68, 0.82)	<0.001

All analyses have adjusted for site as a random effect.

Odds ratio of <1 implied less likely to experience the outcome.

Table S7: Days alive and free of organ support by zero-one inflated beta regression in patients hospitalized with acute COVID-19.

	DAF mecha	nical vent	ilation - first 14 days		DAF	RRT - firs	t 14 days	DAF v	asopresso	rs - first 14 days	
	Unadjusted analysis (n=1330)		Adjusted analysis (r	Adjusted analysis (n=1272)		Unadjusted analysis (n=1319)		Unadjusted analysis	(n=1331)	1) Adjusted analysis (n=1275)	
Variable	Mean diff (95% CI)	P	Mean diff (95% CI)	P	Mean diff (95% CI)	P	Mean diff (95% CI) P	Mean diff (95% CI)	P	Mean diff (95% CI)	P
Wave											
2 vs 1	1.20 (0.06, 2.29)	< 0.001	1.39 (0.29, 2.41)	< 0.001	0.06 (-1.01, 0.94)	0.910	-	0.43 (-0.71, 1.35)	0.177	0.49 (-0.61, 1.44)	0.111
3 vs 1	2.20 (1.09, 3.21)	< 0.001	2.32 (1.28, 3.33)	< 0.001	0.76 (-0.37, 1.70)	0.141	-	1.34 (0.31, 2.27)	< 0.001	1.30 (0.20, 2.19)	<0.001
3 vs 2	1.00 (0.19, 1.74)	0.013	0.94 (0.14, 1.62)	0.017	0.71 (-0.02, 1.47)	0.063	-	0.91 (0.16, 1.74)	0.014	0.81 (0.05, 1.60)	0.026
Male			-0.38 (-0.93, 0.22)	0.185			-			-0.25 (-0.79, 0.31)	0.365
Age (per 10 years increase)			-0.57 (-0.80, -0.35)	< 0.001			-			-0.73 (-0.95, -0.54)	< 0.001
SBP (per 10mm Hg increase)			0.12 (-0.01, 0.24)	0.066			-			0.12 (-0.00, 0.24)	0.043
Chronic kidney disease			0.30 (-0.78, 1.16)	0.469			-			0.22 (-0.76, 1.11)	0.552
Chronic cardiac disease			0.13 (-0.62, 0.81)	0.689			-			0.02 (-0.67, 0.64)	0.944
Diabetes			-0.89 (-1.56, -0.23)	0.004			-			-0.66 (-1.30, -0.08)	0.023
Hypertension			0.27 (-0.39, 0.95)	0.344			-			0.33 (-0.27, 0.94)	0.213
Heart rate (per 10 beats/minute											
increase)			-0.28 (-0.45, -0.13)	<0.001			-			-0.28 (-0.44, -0.13)	<0.001
Creatinine (per log µmol/L increase)			-0.98 (-1.60, -0.40)	0.001			-			-0.96 (-1.53, -0.35)	0.001
Oxygen saturation - SaO2 (per 5 %		•		•							
increase)			0.55 (0.39, 0.73)	<0.001			-			0.45 (0.30, 0.60)	0.001

^{*} Adjusted regression analysis was not feasible numerically as too few patients used RRT during the first 14 days and so most DAF values were 0 or 14.

Estimated difference of >0 implied **more** days alive free of organ support (i.e., better outcome).

All analyses have adjusted for site as a fixed effect.

Table S8: Results from adjusted regression analysis restricting to BC data.

	28-day mortalit	ty	In-hospital death			
Variable	Odds ratio (95% CI)	P	Odds ratio (95% CI)	Р		
Wave						
2 vs 1	0.71 (0.35, 1.41)	0.325	0.60 (0.31, 1.18)	0.138		
3 vs 1	0.33 (0.14, 0.80)	0.014	0.30 (0.13, 0.66)	0.003		
3 vs 2	0.47 (0.22, 1.00)	0.049	0.49 (0.25, 0.97)	0.041		

	Mechanical ventila while hospitaliz		RRT – while hospitalize	ed	Use of vasopressors – while hospitalized		
Variable	Odds ratio (95% CI)	Р	Odds ratio (95% CI)	Р	Odds ratio (95% CI)	P	
Wave							
2 vs 1	0.31 (0.19, 0.52)	<0.001	0.36 (0.11, 1.16)	0.087	0.38 (0.23, 0.63)	<0.001	
3 vs 1	0.22 (0.12, 0.40)	<0.001	0.18 (0.03, 0.96)	0.044	0.32 (0.18, 0.58)	<0.001	
3 vs 2	0.71 (0.42, 1.21)	0.208	0.50 (0.10, 2.45)	0.391	0.86 (0.52, 1.42)	0.554	

	Mechanical ventila first 14 days		RRT- first 14 days		Use of vasopressors – first 14 days		
Variable	Odds ratio (95% CI)	Р	Odds ratio (95% CI)	Р	Odds ratio (95% CI)	P	
Wave							
2 vs 1	0.31 (0.19, 0.52)	<0.001	0.46 (0.10, 2.14)	0.321	0.37 (0.22, 0.63)	< 0.001	
3 vs 1	0.22 (0.12, 0.40)	<0.001	0.37 (0.06, 2.45)	0.303	0.33 (0.18, 0.59)	< 0.001	
3 vs 2	0.69 (0.41, 1.18)	0.177	0.81 (0.15, 4.34)	0.805	0.88 (0.54, 1.46)	0.632	

	DAF mechanical vent first 14 days		DAF vasopressors – first 14 days		
Variable	Odds ratio (95% CI)	P	Odds ratio (95% CI)	Р	
Wave					
2 vs 1	1.61 (0.47, 2.80)	0.001	0.91 (-0.07, 1.87)	0.070	
3 vs 1	2.59 (1.36, 3.76)	< 0.001	1.63 (0.64, 2.60)	0.002	
3 vs 2	0.98 (0.18, 1.71)	0.024	0.73 (0.05, 1.41)	0.037	

Adjusted analysis has accounted for age, sex, chronic heart disease, hypertension, chronic kidney disease, diabetes, baseline systolic blood pressure, baseline heart rate, baseline SaO2, baseline creatinine and site.

Analysis for DAF RRT was not feasible due to low event rate.